Regulated expression of amyloidogenic immunoglobulin light chains in mice

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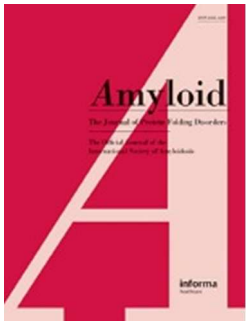

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Regulated expression of amyloidogenic immunoglobulin light chains in mice.

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Background. In immunoglobulin light chain (AL) amyloidosis, clinical and experimental observations converge towards a direct toxic role of the amyloidogenic light chain (aLC) precursor [1, 2, 3]. However, the molecular underpinnings of AL amyloidosis remain obscure, partly due to the paucity of preclinical models for this disease. Generation of conventional transgenic mice with constitutive overexpression of human aLCs is technically hampered by the potential toxicity of these proteins, possibly resulting in embryolethality and selection against high expressor lines [4]. To overcome these limitations, we have employed the Cre/loxP system to generate a conditional transgenic mouse allowing regulated expression of an aLC.

Materials and methods. The cDNA encoding a human aLC (λ), termed MAB, was sub-cloned in the pCAG-CAT-Oligo vector [5]. The resulting expression vector consisted of (5'→3'): a ubiquitous promoter (CAG), a reporter gene-stop cassette (CAT) flanked by two equally oriented loxP sites and the aLC (MAB). Transgenic mice obtained by pronuclear injection in C57BL/6J fertilized oocytes (termed CAG-CAT-MAB) were crossed with either mice expressing a constitutively active cre recombinase under the albumin promoter (Alb-cre) [6], or with mice expressing a tamoxifen-inducible cre recombinase under the CAG-promoter (CAGGS-cre^{TM}) [7]. Expression of human aLCs was analyzed by RT-PCR, immunohistochemistry, Western blotting and ELISA.

Results. Pronuclear injection of the CAG-CAT-MAB vector resulted in the generation of three transgenic lines. CAG-CAT-MAB$^{Tg/+}$ mice showed ubiquitous expression of the CAT reporter gene, but no expression of aLC, as expected. Crossing with Alb-cre transgenic mice resulted in hepatocyte-restricted expression of aLC, whereas crossing with CAGGS-cre ^{TM} transgenic mice lead to ubiquitous expression of aLC after tamoxifen administration (Figure 1). Human aLC could be detected in serum, and mice with ubiquitous expression show higher levels than mice with hepatocyte-restricted expression. Mice with hepatocyte-restricted expression of aLC have been monitored for up to two years, with no evidence of amyloid formation.

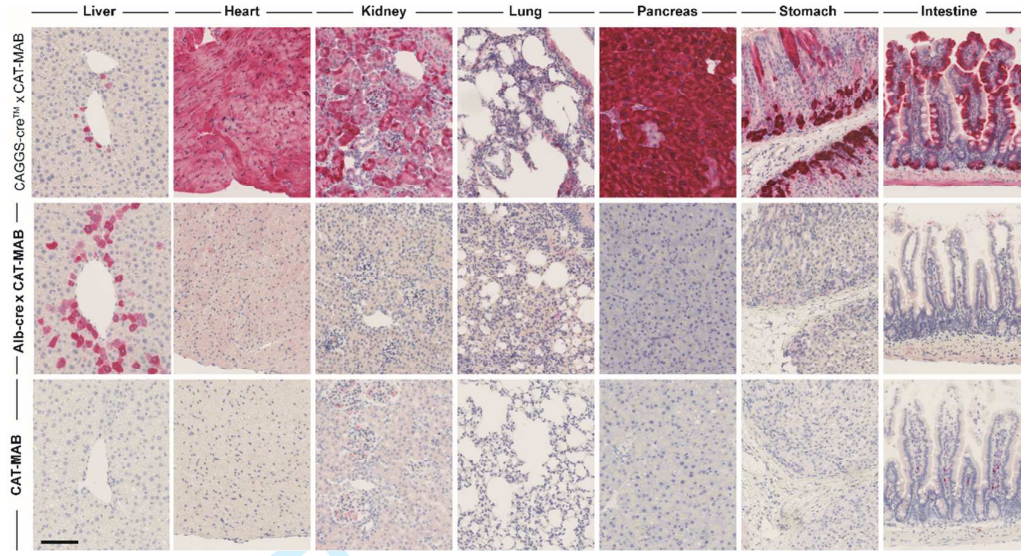

Figure 1. Regulated expression of amyloidogenic immunoglobulin light chains in mice. Immunohistochemical analysis of human λ expression (in red). Scale bar: 100 μm.

Discussion and conclusions. We have generated a novel transgenic mouse in which the expression of aLC can be activated in a spatially and temporally regulated manner. In mice with hepatocyte-restricted expression of aLC, all target organs (except the liver) are exposed to aLC exclusively coming from the circulation, resembling the clinical situation. Ubiquitous expression of aLC results in higher levels of circulating aLC. Additional cre transgenic lines can be used to further manipulate the temporal and spatial pattern of aLC expression. This newly developed conditional transgenic mouse could prove instrumental to deepen our current mechanistic understanding of AL amyloidosis.

Declaration of interest. The authors have no conflict of interest to report.

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